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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,033	11/27/2002	H. Michael Shepard	NB 2006.01	2767

23639 7590 09/29/2005

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EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/048,033	SHEPARD, H. MICHAEL	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20-25* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/12-13/05(3)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SW

The Abstract of the Disclosure is objected to because is does not meet the requirement of the MPEP for US application. Correction is required. See MPEP 608.01(b).

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts, compounds or compositions, the general nature and chemical structure of the compound or composition should be given as well as its use, e.g., "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of the structure of a species should be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet in order to comport with standard USPTO practice..

This application has been filed with drawing labelled "Figure 6" which includes at least two serious technical errors. Applicant is requested to note that according to the disclosure NB-1011, as a phosphoramidate analog of 5-bromovinyluridine-5'-monophosphate, must be a uridine with C=O groups at heterocyclic ring positions 2 and 4 while the present Figure 6 includes exocyclic vinyl groups at the 2-position in the first two structures. Correction of all errors in Figure 6 is respectfully requested.

The instant disclosure fails to include "Cross-References to Related Applications." See 37 C.F.R. §1.78 and MPEP at §201.11. Applicant is respectfully requested to include the requested information as the first paragraph of the disclosure including the status of the instant application as a 371 filing based on a PCT priority document. In addition, examiner respectfully requests a complete and comprehensive listing of all of the US patent applications directed to overlapping subject matter which have been filed in the name of applicant Shepard.

The application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §1.821 through §1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given **3 (THREE)** MONTHS from the date of this letter within which to comply with the sequence rules, 37 C.F.R. §1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. §1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. §1.136. In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Applicant is requested to return a copy of the attached Notice To Comply with the response.

Applicant is referred to the nucleotide sequences at pages 52 and 54 of the instant application's specification.

No claims have been cancelled, no claims have been amended, the disclosure has not been amended, no new claims have been added, and no preliminary amendments have been filed as of the date of the mailing instant Office action. Three Information Disclosure Statements (3 IDSs) filed January 12, 2005 (1) and January 13, 2005 (2) have been received with a large number of cited references and made of record.

Claims **1-25** remain in the case.

The disclosure is objected to because of the following informalities:

At page 43, lines 24, the term "C4 hydozone" is apparently a misspelling of the term -- C4 hydrazones --. Appropriate correction is respectfully requested.

Appropriate correction is required.

Claims **2, 3 and 19** are objected to because of the following informalities:

Claim **2** does not have a preamble and therefore appears to be a compound claim. The only way this claim is identified as a "method claim" is by the definition of claim **3** as " [t]he method of claims **1 and 2** ... ." Also, at the last line of claim **2** the term "and any 2, B." is either an incomplete statement of what applicant intended or is a typographical error. Applicant is respectfully requested to provide a complete version of claim **2**.

In claim **3** at line 4, the second structure in incomplete or contains a valence error because the ring nitrogen between the ring carbonyl groups is divalent. Did applicant intend

the noted nitrogen to read
-- -N(H)- --? See also the structure labelled "IV" for the same error.

In claim **3** at line 11, the end of the line includes inappropriate terminal punctuation. Deletion or replacement is respectfully suggested.

In claim **3** at line 35, the side chain of the substituent,
"- NH-C(=O)-CH_2," includes what appears to be a valence error. Did applicant intend the term to read -- - NH-C(=O)-CH_3 -- (?) or is there a missing substituent which applicant has failed to include and to define as part of the noted substituent? Submission of an appropriate clarifying amendment is respectfully suggested.

In claim **3** at lines 20-24, 31-42 and 50-51, there is no punctuation separating members of the Markush groups. In addition at line 21 the term "and" should be replaced by punctuation, and at line 23, the term
-- and -- should be inserted between the last two Markush groups members.

In claim **3** at lines 50-51, applicant is respectfully requested to increase the size of the fonts and/or change the particular font of the superscript numbers to insure that the claim is legible; presently the scanning process has made the number 6 easily confused with the number 8.

In claim **19** at line 1, the term (e) is technically incorrect. Did applicant intend the term to read (E)?

Appropriate correction is required.

Claim **19** is objected to under 35 C.F.R. §1.75(c), as being in improper dependent form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP §608.01(n). Accordingly, claim **19** has not been further treated on the merits.

Claims **1-18 and 20-25** remain under examination.

Claims **20-25** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant disclosure makes reference to liquid chromatography/mass spectrometry (LC/MS) in a single short paragraph bridging pages 56 and 57 but fails to provide adequate detailed guidance therein to disclose to one of ordinary skill how this analytical tool can be used to execute the method of claims **20-25**. Examiner has found no further reference to LC/MS or its application to the analysis method of the instant claims in the remainder of the disclosure. Similarly fluorescence detection is briefly mentioned at page 56, lines 15-19, of the disclosure, but the specifics of its application to achieve the method of claims **20-25** do not appear to have been provided therein or elsewhere within the disclosure. Based on these observations examiner believes there is a serious question as to whether the method of claims **20-25** was actually in the possession of the instant applicant as of the instant date of filing.

Claims **1-18** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention; the scope is excessive in view of the disclosed exemplifications.

The subject matter of claims **1-18** as defined by independent claim **1** and in completely presented dependent claims **3-18** are defined by a plethora of functional terms and by a vast array of possible chemically defined active ingredients which define a scope of subject matter which is simultaneously indefinite (see rejections under 35 U.S.C. §112, second paragraph below) and inadequately supported by the specific embodiments. The instant disclosure only discloses the medicinal activity of a single compound (NB1011) against a single type of chemotherapy effective in a limited number of neoplastic disease conditions which are characterized in part by cells which overexpress thymidylate synthase activity. The absence of sufficient test data renders extrapolation to other neoplastic disease conditions wherein other overexpressions of different enzymatic activities makes extension of the scope of enabled subject matter unsupportable. In the absence of a substantial increase of disclosed test data (declaration(s) under 37 C.F.R §1.132 ?), examiner suggests that the instant claims need to be limited to a scope supportable by the very limited disclosure of compounds shown to have activity against neoplastic disease cells characterized by thymidylate synthase over-expression. Claim **19**, were it under examination, would also be rejected for the reasons noted.

Claims **1-3, 6, 12-14, 17, 18 and 20-25** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **1** at line 1, the term "selectively inhibiting a pathological cell" is functional language which renders the instant claim incomplete because it fails to define the particular disease condition(s) to be treated and fails to specify that the host "cell" is -- in need thereof --.

In claim **1** at lines 2-3, the term "characterized by overexpression of an endogenous, intracellular activating enzyme and wherein the enzyme is not activated by a substrate prodrug compound" is indefinite because it fails to define the enzyme being overexpressed, and it fails to define by chemical name, by specific structure, or by generic structure with variables defined, the particular compound(s) being referred to by the included negative limitation, thereby rendering the claim incomplete.

In claim **1** at lines 4-5, the term "the substrate compound having the structure selectively converted to a toxin in the cell by an activating enzyme" is an entirely functional term which renders the instant claim incomplete because it fails to define by chemical name(s), by specific structure(s), or by generic structure with variables defined, the particular compounds(s) which is/are necessarily present to effect the claimed treatment.

In claim **2** at line 2, the three chemical formulas provided are related as tautomers, with the second and third structures being superfluous in view of the first structure because any ordinary practitioner of heterocyclic chemistry will know that amido-imido tautomeric equilibria will govern the location of the hydrogen found at N-3 of the first structure. Therefore, the second and third structures are unnecessary and their deletion is respectfully requested.

In claim **2** at lines 3-6, the definition of variable "R_1" is entirely functional and thereby renders the claim incomplete because R_1 has not been defined by chemical name(s), by specific structure(s), or by generic structure with variables defined. The noted lines appear to be a partial description of a biomolecular mechanism and as such, said lines are in a sense also superfluous because the formation of -- metabolites -- inside the body of a host is not subject to any patent claims because said claims are barred by the 13th and 14th Amendments to the US Constitution which Amendments prohibit the ownership of any human being by another. Examiner suggests respectfully that the noted functional term needs to be replaced by chemical formula(s), generic or specific, which entirely identify the metes and bounds of the chemical and biochemical characteristics of the noted substituent which is/are necessarily present in the active ingredient prior to administration.

In claim **2** at lines 7-8, the definition of variable "Q" is incomplete because the particular substituent groups intended are not and literally cannot be "a sugar," "a carbocyclic," "an alicyclic compound," " a masked phosphate," or "phosphoramidate derivatives" because most if not all of the noted terms actually define or appear to define separate compounds. Examiner respectfully requests that the chemical substituent group "Q" to be defined by structure in a manner which specifies the attachment point of the group to the generic structures at lines 4 and 7 and all of the structural particulars within the intended metes and bounds of the substituent.

In claim **3** at line 12, the term "electron conduit moiety" is unfamiliar terminology. Applicant is respectfully requested to either deleted the included term "electron conduit" or provide a clear explanation of what is meant by the initially noted term.

In claim **3** at lines 12-18, the definition of variable "R_2" is incomplete because the terms used to define said variable are lacking in any upper bounds and also lacking in structural specifics. Additionally, the included term "comprising" renders the metes and bounds of the parts of the noted definition where said term is found indefinite because said term implies that said definitions are incomplete; i.e. that the definition "includes" more structural variations than those specifically stated in the definition. Examiner respectfully suggests that the verbal-only definitions need to be replaced with chemical structures in all parts of the instant definition.

In claim **3** at lines 9-18, the definition of R^1 and the definition of R^2 are inconsistent because R^2 appears to be defined as a terminal substituent while such a possibility is not provided for in the definition of variable R^1. Because the only enabled embodiment requires R^2 to be a terminal substituent, a clarifying amendment is necessary if applicant intends to insure that NB1011 is encompassed within the metes and bounds of claim **3** as a possible active ingredient. Examiner suggests further that the definition of R^2 needs to be made more detailed to insure that the C-5 substituent of NB1011 has been included; i.e. the "unsaturated hydrocarbyl group" needs to be amended to include the possibility of terminal halogen substitution on a vinyl group.

In claim **3** at line 44, the term "other potent leaving group" lacks metes and bounds because it fails to define with particularity the identity of the "leaving groups" being referred to.

In claim **3** at lines 44-46, applicant is respectfully requested to move all provisos to the end of the claim to insure clarity of meaning and to minimize confusion concerning which portions of the claim are included within the provisos.

In claim **3** at lines 52-53, the term "or other protected hydroxyl group" is unclear and/or an incomplete description of what applicant intended to claim. Clarification is respectfully requested.

In claim **3** at lines 54-55, the terms "phosphodiester group" and "phosphoramidate group" are incomplete because the first term has not been further defined as to the second substituent which makes it a "diester," and the second term is incomplete for failure to define whether the nitrogen of the phosphoramidate is located between the phosphorus atom and the CH_2 group of Q or is located elsewhere and is also incomplete for failure to define the other substituents which must be present for the compound NB1011 to be included within the metes and bounds of the claim.

In claim **3** at lines 56-58, the term "including" is incorrect because it suggests that there are other possibilities which have not been listed thereby rendering the metes and bounds of the claim indefinite. Examiner notes that applicant has not listed geometric isomers (E and Z).

In claims **6 and 13** the term "Tomudex" appears to be either a tradename or a trademarked name. Applicant is respectfully requested to replace same with the a complete chemical name in order for the claim to be complete. In addition the term "fluoropyrimidine" is incomplete because the particular compound or compounds intended to be encompassed by said term has/have not been defined by the claim.

In claim **12** the term "a second therapeutic agent" is incomplete because the identity of said agent(s) has not been specified, thereby rendering the metes and bounds of the noted claim indefinite.

In claim **14** the term "*in vitro*, *ex vivo* and *in vivo*" is unusual and would appear to require simultaneous contact of all three types. Did applicant intend to list the noted terms in the alternative (replace "and" with -- or --- in the noted term)?

In claim **17** the term "a compound that diminishes intracellular thymidine or purine" is incomplete because the identity of said compound has not been specified, thereby rendering the

metes and bounds of the noted claim indefinite. In addition the term "purine" is generic and may refer to several different nucleic acid bases, nucleosides and/or nucleotides found in cells, thereby rendering the instant claim indefinite for failure to define with particularity the compounds the concentrations of which are being suppressed.

In claim **18** the term 6-mercaptopurein" appears to be a misspelling of the term -- 6-mercaptopurine --. Clarification is respectfully requested.

Claims **20, 21 and 25** should be combined in order to properly describe the test protocol being claimed: claim **20** is presently misleading because said claim fails to make clear that the two cells must be different and that one must be normal and the other non-normal for the test to be effective.

Claim **23** is confusing because it is unclear whether a single compound or two different compounds are being referenced by the terms "candidate agent" and "detectable agent."

In claim **24** the term "detectable agent is a fluorescent marker" is technically inconsistent and therefore confusing because a fluorescent marker may be either a separate compound or a substituent group. Clarification is respectfully requested.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-12** of U. S. Patent No. **6,495,553**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **36-39** of U. S. Patent No. **6,339,151**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-7** of U. S. Patent No. **6,245,750**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **56-84 and 86-89** of co-pending Application No. **09/782,721** (for the PG Pubs version, see PTO-892 ref. **P1**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **15-18, 21-23 and 27-50** of co-pending Application No. **09/789,226**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-36** of co-pending Application No. **11/034,036**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-18** of co-pending Application No. **10/051,320** (for the PG PUBS version, see PTO-892 ref. **P3**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1 and 53-83** of co-pending Application No. **10/681,418**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Claims **1-25** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-10** of U. S. Patent No. **6,683,061** (PTO-892 ref. **AB**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

One or more of claims **1-25** of this application conflict with claims **1-33** of Application No. **10/119,927**, claims **56-84 and 86-89** of Application No. **09/782,721**, claims **1-18** of co-pending Application No. **10/051,320**, claims **1 and 53-83** of co-pending Application No. **10/681,418**, claims **1-36** of copending Application No. **11/034,036**, and claims **15-18, 21-23 and 27-50** or copending Application No. **09/789,226**. 37 C.F.R. §1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of

such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP §822.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

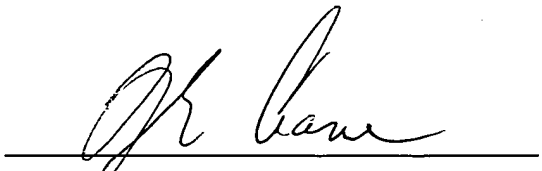
Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
09/21/2005



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